

ORIGINAL ARTICLE

A Form of the Metabolic Syndrome Associated with Mutations in *DYRK1B*

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ABSTRACT

BACKGROUND

Genetic analysis has been successful in identifying causative mutations for individual cardiovascular risk factors. Success has been more limited in mapping susceptibility genes for clusters of cardiovascular risk traits, such as those in the metabolic syndrome.

METHODS

We identified three large families with coinheritance of early-onset coronary artery disease, central obesity, hypertension, and diabetes. We used linkage analysis and whole-exome sequencing to identify the disease-causing gene.

RESULTS

A founder mutation was identified in *DYRK1B*, substituting cysteine for arginine at position 102 in the highly conserved kinase-like domain. The mutation precisely cosegregated with the clinical syndrome in all the affected family members and was absent in unaffected family members and unrelated controls. Functional characterization of the disease gene revealed that nonmutant protein encoded by *DYRK1B* inhibits the SHH (sonic hedgehog) and Wnt signaling pathways and consequently enhances adipogenesis. Furthermore, *DYRK1B* promoted the expression of the key gluconeogenic enzyme glucose-6-phosphatase. The R102C allele showed gain-of-function activities by potentiating these effects. A second mutation, substituting proline for histidine 90, was found to cosegregate with a similar clinical syndrome in an ethnically distinct family.

CONCLUSIONS

These findings indicate a role for *DYRK1B* in adipogenesis and glucose homeostasis and associate its altered function with an inherited form of the metabolic syndrome. (Funded by the National Institutes of Health.)

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